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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,020	09/29/2003	Stephen Donovan	17510DIV1 (BOT)	4829

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STEPHEN DONOVAN
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,020	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-21 and 36-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-21 and 36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive to Applicant's amendment and response filed May 9, 2008 is acknowledged. Claims 1-15 and 22-35 have been cancelled. Claim 37 has been amended. Claims 16-21 and 36-45 are pending and under examination in this office action. A new Non-Final action is set forth below:

Rejections Withdrawn

2. In view of Applicant's amendment and remarks the following objection/rejections are withdrawn:

(a) objection to claim 37, page 2, paragraph 2 of the previous Office action.

(b) rejection under 35 U.S.C. 103(a) for claims 16-21, 39-40 and 44-45 , pages 3-6, paragraph 3 of the previous Office action.

(c) rejection under 35 U.S.C. 103(a) for claims 36-38 and 41-43, pages 6-9, paragraph 4 of the previous Office action.

New Grounds of Rejection

Claim Objection

3. Claim 20 is objected to for the following informality: "ad" should be changed to "and". Correction is required.

4. Claim 39 is objected to for the following informality: "wit" should be changed to "with". Correction is required.

5. Claim 40 is objected to for the following informality: "les" should be changed to "less". Correction is required.

6. Claims 16-21, 39-40 and 44-45 are rejected under 35 U.S.C. 103(a) as unpatentable over Hymes et al *(U.S. Patent No. 4, 675, 009 issued June 23, 1987)* in view of Pearce et al *(U.S. Patent No. 6,087327 issued July 11, 2000)* in view of Mohr et al (*U.S. Patent No. 5,591,767 published January 7, 1997)* and in further in view of Yuzhakov et al *(U.S. Patent No. 6.565,532 B1 published May 20, 2003).*

Independent claim 16 is drawn to a transdermal patch comprising (a) a pharmaceutical composition comprising: i) a stabilized botulinum toxin provided in a dried state; and ii) an enhancing agent that is mixable with the stabilized botulinum toxin provided in a dried state and facilitates transdermal administration of a botulinum toxin in a bioactive form to a subdermal target site of a human patient without being administered to the patient's circulatory system; and b) an adhesive disposed to one side of the transdermal patch to removably secure the patch in the patient's skin; wherein the pharmaceutical composition is incorporated into the adhesive layer and wherein upon contacting with a fluid, the fluid solubilizes the pharmaceutical composition, thereby permitting diffusion of the pharmaceutical composition form the adhesive layer.

Hymes et al teach a flexible, liquid –absorbing, adhesive skin reservoir composed of a matrix containing polymer a polysaccharide and contains a medicament (a transdermal patch) (see the Abstract). Hymes et al teach that the reservoir contains a self-adhesive substrate (column 1). Hymes et al teach that the skin reservoir also contains a hydrophilic substance which moisturizes the skin and enhances absorptions of the medicament (such as glycerol or alcohol) (columns 2 and 4-5). Hymes et al teach that the reservoir can contain any number of medicinal substances (column 3).

Hymes et al do not teach a stabilized botulinum toxin in the dried state.

Pearce et al teach depots of botulinum toxin stabilized with gelatin to be used in pharmaceutical compositions (column 9). Pearce et al teach that the botulinum toxin compositions are dried (columns 8-9). Pearce et al teach that the depots of the invention can be used in transdermal diffusion (column 9). Claim limitations such as "facilitates transdermal administration of a botulinum toxin in a bioactive form to a subdermal target site of a human patient without being administered to the patient's circulatory system" (claim 20), "the transdermal patch of claim 39, wherein less than 25% of the administration botulinum toxin permeates into blood vessel" (claim 40) would be necessarily taught by the in the combination of prior art references since the botulinum botulinum toxin compositions are used for transdermal delivery.

Hymes et al and Pearce et al do not teach the claim limitation "wherein the pharmaceutical composition is incorporated into the adhesive layer" and "wherein upon contacting with a fluid, the fluid solubilizes the pharmaceutical composition, thereby permitting diffusion of the pharmaceutical composition form the adhesive layer".

Mohr et al teach transdermal patches that are adhesive matrix patches where the drug and the enhancer are formulated into the skin adhesive layer (column 7). Mohr et al teach that the adhesive layer serves both as the and enhancer reservoir as well as the adhesive layer which attaches the patch to the patient's skin (column 7).

Hymes et al nor Pearce et al or Mohr et al teach the claim limitation "the transdermal patch of claim 16, further comprising a plurality of needles extending from one side of the patch that is applied to the skin, wherein the needles extend from the patch to project through the stratum corneum of the skin without rupturing a blood vessel" (claim 18).

Yuzhakov et al teach that the transdermal patch contains a microneedle array (column 3). Yuzhakov et al teach that the invention is projected or penetrates the stratum corneum (column 3).

It would be *prima facie* obvious at the time the invention was made to modify the skin reservoir (e.g. transdermal patch) as taught by Hymes et al to incorporate the botulinum toxin as the medicament as taught by Pearce et al into the adhesive layer according to Mohr et al and include the needle array as taught by Yuzhakov et al because Mohr et al has demonstrated that this design of transdermal patch is simple but yet effective in delivering drugs to the skin and Yuzhakov et al teach that the invention is projected or penetrates the stratum corneum to transfer active agents to the skin (column 3). It would be expected, absent evidence to the contrary, that incorporating a drug and an enhancing agent into the adhesive layer of a transdermal patch as taught by Mohr et al and incorporating needle array, wherein the needles

deliver pharmaceutical compositions to patient's skin as taught by Yuzhakov et al into skin reservoirs (transdermal patches) containing skin enhancers and botulinum toxin as taught by Hymes et al and Pearce et al combined above would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of a patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method , and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art to use stabilized dried botulinum toxin for transdermal delivery. See Pearce et al. It is also known in the art to use a skin reservoir or transdermal patch to deliver medicaments transdermally. See Hymes et al. It is known in the art to formulated the active drug or medicament and the enhancer into the skin adhesive layer of the transdermal patch. See Mohr et al. It is further known in the art to penetrate the stratum corneum to transfer actives or skin support structures to the epidermis. See Yuzhakov et al.

Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness absent convincing evidence to the contrary.

7. Claims 36-38 and 41-43 are rejected under 35 U.S.C. 103(a) as unpatentable over Hymes et al, Pearce et al, Mohr et al and Yuzhakov et al as applied to claims 16-21, 39-40 and 44-45 above and further in view of Cevc *(U.S. Patent No.6,165,500 published December 26, 2000).*

Dependent claims 36-38 and 41-43 are drawn to "the transdermal patch of claim 16 wherein the enhancing agent comprises 1 part water, 1 part ethanol and 2 part polyethylene glycol"(claim 36), "the transdermal patch of claim 36 wherein is 90% ethanol"(claim 37) and "the transdermal patch of claim 16, wherein the enhancing agent comprises 1 part of 10% transfersomes and 0.9 part of a buffer" (claim 38).

The teachings of Hymes et al, Pearce et al, Mohr et al and Yuzhakov et al have been described previously.

Hymes et al, Pearce et al, Mohr et al and Yuzhakov et al do not teach the limitations of claims 36-38 and 41-43 which are " the transdermal patch of claim 16 or 39, wherein the enhancing agent comprise 1 part water, 1 part ethanol, and 1 part polyethylene glycol", "the transdermal patch of claim 16 or 39, wherein the enhancing agent comprises 1 part of 10% transfersomes and 0.9 part of a buffer" and "the transdermal patch of claim 36 or 39 wherein the ethanol is 90% ethanol".

Cevc teaches that solvents such as ethanol (enhancing agents) can be used to induce or increase the carrier system's capacity to form edges, protrusions or relatively strongly curved surfaces; this property also manifests itself in the capability to induce pores in lipid structures, such as membranes, or even provoke a solubilization (lysis) in

the higher concentrations ranges (columns 7-8). Cevc teaches that the transfersome compositions of the invention can be introduced not only to a permeability barrier such as the skin (column 4, 66-67 and column 5, lines 1-4). Cevc teaches compositions that comprise transfersomes ranging in concentration from 0.1 to 99% of the total composition (column 4, lines 47-56) Cevc teaches the use of edge active substances used in the transfersomes such as polyethylene glycol (columns 7-9). Cevc teaches buffer such as Hepes (column 55). Cevc teaches that the ethanol use to in the claimed invention is absolute ethanol (columns 55-56), therefore the ethanol taught by the prior art teaches the claim limitation “wherein the ethanol is 90% ethanol”.

Regarding the specific concentrations listed in the instant claims,

> MPEP 2144.05 states, “Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).”

It would have been *prima facie* obvious at the time the invention was made to modify the transdermal patch as taught by Hymes et al Pearce et al , Mohr et al and Yuzhakov et al as combined above to include transfersomes in the enhancing agent because Cevc teaches compositions that comprise transfersomes ranging in concentration from 0.1 to 99% of the total composition (column 4, lines 47-56), the use of edge active substances used in the transfersomes such as polyethylene glycol (columns 7-9) and the use of buffers such as Hepes (column 55). Cevc also teaches that the ethanol used in the claimed invention is absolute ethanol (columns 55-56), therefore the ethanol taught by the prior art teaches the claim limitation "wherein the ethanol is 90% ethanol". It would be expected barring evidence to the contrary, that incorporating transfersomes into transdermal patches of Hymes et al, Pearce et al, Mohr et al and Yuzhakov et al combined above and the transfersomes would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of a patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, it would be obvious to combine the skin reservoir (transdermal patch) and enhancer as taught by Hymes et al

with the stable dried botulinum toxin depot as taught by Pearce et al, the incorporation of a drug and enhancing agent within the adhesive layer of a transdermal patch as taught by Mohr et al, the incorporation of a needle array, wherein the needles deliver pharmaceutical compositions to patient's skin as taught by Yuzhakov et al and the transfersomes as taught by Cevc because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), disclosed that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness absent convincing evidence to the contrary.

Status of Claims

8. No claims allowed.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Patent Examiner, Art Unit 1645
July 15, 2008